8.7 A Current-Sensitive Front-End Amplifier for Nano-Biosensors with a 2MHz BW

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Electrical characterization of single molecules and nanometer-scaled devices requires special care because of their very small dimensions and poor conductances. The signal to be detected, in the majority of cases being a current, is extremely low and often reaches the pA range in the nano-bio research field [1,2]. To measure these values, very low-noise and high-sensitivity front-end preamplifiers are needed. In addition, to be able to track the time evolution of a biological system the preamplifiers need fast settling times (i.e., relatively large bandwidths). For example, to detect the chemical identity of single molecules passing through an ion channel one should discriminate ionic current variations on the tens-of-microseconds time-scale [3], wich corresponds to a bandwidth of 100kHz.

When wide bandwidth and high sensitivity are required in current detection, the best performance is obtained by the integrator-differentiator transconductor whose scheme is illustrated by the black lines in Fig. 8.7.1. The absence of physical resistors at the input node ensures minimum noise; the noise is just that of the differentiator stage reduced by the factor $(C_d/C_i)^2$. In many practical cases the bandwidth of the circuit is given by GBP$\cdot C_i/(C_i + C_s)$, where GBP is the gain-bandwidth product of the operational amplifier OP_{int} and C_s is the total capacitance at the input node of the integrator stage. A bandwidth in the MHz range can be obtained by choosing C_i on the same order as C_s.

The disadvantage of this class of instrument is that the feedback capacitance of the integrator stage, C_i, must be discharged to prevent its saturation due to the input leakage current. Obviously a simple feedback resistor in parallel with C_i cannot be used in an integrated realization because of the large value required to minimize noise. Few commercial current sensing amplifiers intended for bio-electronic applications based on the scheme of Fig. 8.7.1 are available in the form of lab-instruments [4]. To prevent saturation, such instruments are provided with a MOSFET switch placed in parallel with the integrator capacitor C_i, which discharges it when the output voltage reaches a defined threshold. This switch sets a limit to the measurement time available, which depends on both the input leakage current and C_i. This issue makes such solutions impossible to integrate, since the unavoidable reduction of the integrator capacitor, required to enhance sensitivity, makes the discharge period too small: a 10nA leakage current with 100fF feedback capacitor would result in a reset every 10µs.

This paper presents a circuit solution, shown by the gray lines in Fig. 8.7.1, that allows continuous operation of the current-to-voltage conversion while keeping all the positive features of the integrator-differentiator scheme. The feedback loop has an amplifier $H(s)$ and a transconductor G_{DC}. At very low frequencies (0 to 100Hz), the high gain of amplifier $H(s)$ drives the transconductor G_{DC} in order to keep the integrator's output constant and drain I_{dc} from the integrator stage. At medium frequencies (100Hz to 1MHz), when the capacitive path C_2 and C_1 in the amplifier $H(s)$ becomes dominant, significant attenuation is introduced in the loop, deactivating it and leaving the integrator free to amplify the input current. The amplifier actually has two outputs: a DC output V_{DCout} given by the transconductor G_{DC} that senses the input current with frequencies lower than 100Hz and the signal output V_{ACout} with a bandwidth of 100Hz to 1MHz.

Figures 8.7.2 and 8.7.3 show the measured transfer functions from the input current to V_{DCout} and V_{ACout} respectively. By choosing C_i = 100fF to maximize sensitivity together with a differentiator capacitor C_d = 20pF, we obtain a low noise-current gain of C_d/C_i = 200. The linear transconductor G_{DC} has been conceived as an active circuit using the matched MOSFETs T_{att} and T_{spill}. With negative V_{GS}, the devices operate as diode-connected MOS transistors; with positive V_{GS}, the drain-well junctions are activated, and the transistors act as p-n diodes. Because of the operational amplifiers OP_{att} and OP_{int}, T_{att} and T_{spill} always operate with the same bias conditions and, since T_{att} is sized M = 100 times larger than T_{spil}, the matched MOSFETs reduce the current flowing in R_{att} (made of high resistitive polysilicon element of 300kΩ) by the same factor M. So the thermal noise of R_{att} is reduced by a factor M^2 = 10000, yielding an input noise equivalent to a physical resistor of 3GΩ. Moreover, since the well terminals of the MOSFETs are actively driven, no parasitic currents limit the minimum operative range of the system allowing it to work down to the fA range [5].

In addition to realizing a compact and low-noise transconductor, another key aspect of this circuit is the placement of the $H(s)$ amplifier singularity to ensure stability of the feedback loop. To set the cut-off frequency of the loop gain at about 100Hz, a large capacitive C_1/C_2 attenuation (of about 400 in this case) and very low-frequency singularities (less than 10Hz) are necessary, requiring a resistor R_a of hundreds of GΩ. This resistor is, again, an active device implemented by a cascade of 4 matched MOSFET systems similar to the T_{att}-T_{spill} circuit discussed before, achieving an equivalent resistance of about 300GΩ [5]. This realization ensures a very precise control of the current flowing, down to the fA range as demonstrated by the measurements presented in Fig. 8.7.4. The linearities of the resistance R_a and the transconductance G_{DC} ensures the stability of the feedback loop in all operating conditions.

The integrator stage with DC stabilization network has an equivalent input noise in the signal bandwidth, considering only main terms, given by:

$$\overline{i_n^2} \approx \frac{4kT}{R_{att}M^2} + \overline{i_{Tspil}^2} + \omega^2\left(C_i + C_s\right)^2 \cdot \overline{e_{\text{int}}^2} \quad (1)$$

where $\overline{i_{Tspil}^2}$ is the noise of MOSFET T_{spil} and $\overline{e_{\text{int}}^2}$ is the noise voltage of the operational amplifier OP_{int}. The $\overline{i_{Tspil}^2}$ term is caused by shot noise or thermal channel noise depending on the operating region of transistor T_{spill} (subthreshold or strong inversion, respectively) and is negligible for bias currents smaller than tens of pA. Figure 8.7.5 shows the equivalent input noise measured on the integrator prototype, operating with an input bias current of 10pA. The experimental result is in agreement with the theoretical prediction (dashed line) given by Eq. (1) with an equivalent noise of the amplifier OP_{int} of $\overline{e_{\text{int}}^2} = 4\text{nV}/\sqrt{\text{Hz}}$, and a total input capacitance C_s = 700fF given by the operational amplifier and the input bonding pad. The white noise is confirmed to be very low, corresponding to the thermal noise of a 1GΩ resistor, and the flicker noise is negligible over the entire signal bandwidth.

The prototype was fabricated using a 2P4M 0.35µm CMOS process. The chip micrograph is shown in Fig. 8.7.6. The chip occupies 0.11mm² and consumes 21mW from a 3.3V supply.

References:

[1] P. J. de Pablo et al., "Absence of DC-Conductivity in λ-DNA," *Phys. Rev. Lett.*, vol. 85, pp. 4992–4995, Dec. 4, 2000.

[2] L. Movileanu et al., "Detecting Protein Analytes that Modulate Transmembrane Movement of a Polymer Chain Within a Single Protein Pore," *Nature Biotechnololgy*, vol. 18, pp. 1091–1095, 2000.

[3] M. Akeson et al., "Microsecond Time-Scale Discrimination Among Polycytidylic Acid, Polyadenylic Acid, and Polyuridylic Acid as Homopolymers or as Segments Within Single RNA Molecules," *Biophysical J.*, vol. 77, pp. 3227–3233, Dec., 1999.

[4] Axopatch 200B, Molecular Devices Corporation, www.moleculardevices.com/pages/instruments/cn_axopatch200b.html

[5] F. Gozzini, G. Ferrari and M. Sampietro, "Linear Transconductor with Rail-to-Rail Input Swing for Very Large Time Constant Applications," *Electronics Letters*, vol, 42, Issue 19, pp. 1069-1070, 2006.

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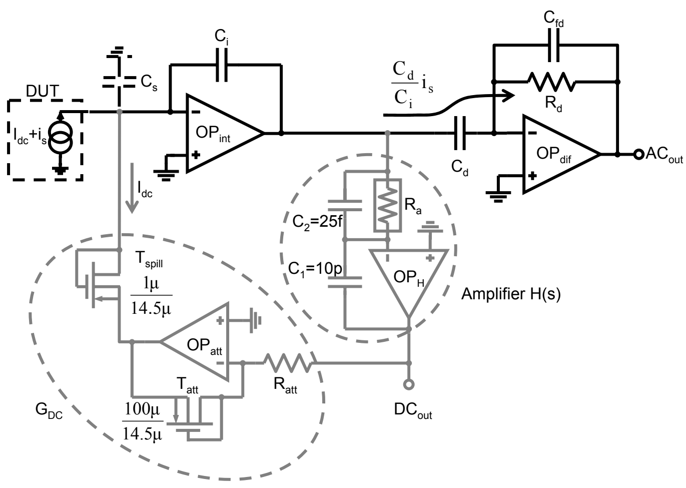

Figure 8.7.1: Integrator-differentiator transimpedance amplifier; the grey lines show the continuous reset circuit presented here.

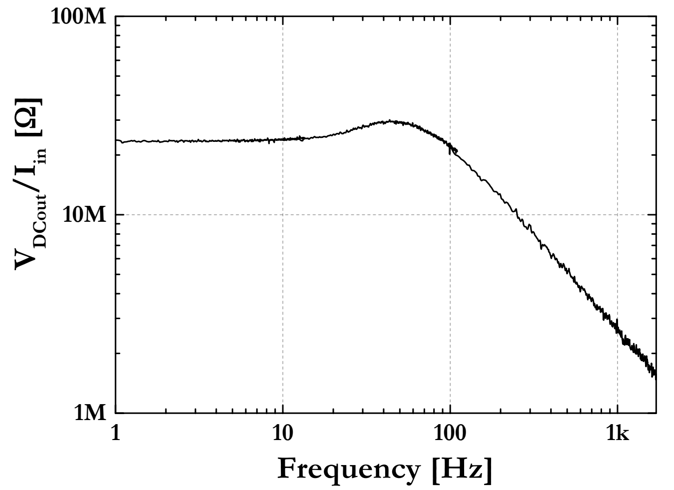

Figure 8.7.2: Measured transfer function for V_{DCout}

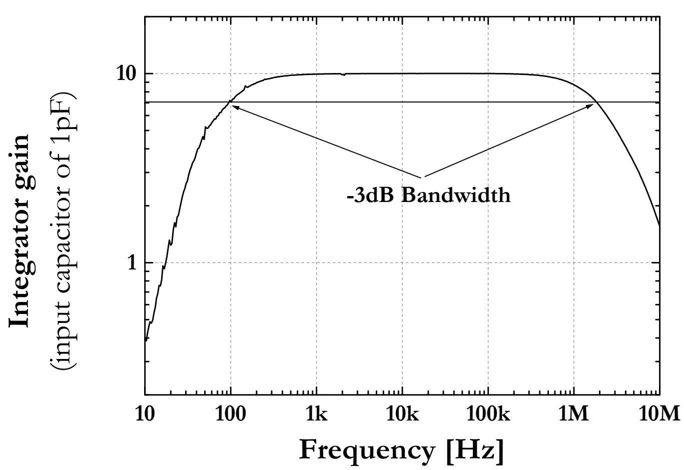

Figure 8.7.3: Measured integrator gain with a 1pF input capacitor.

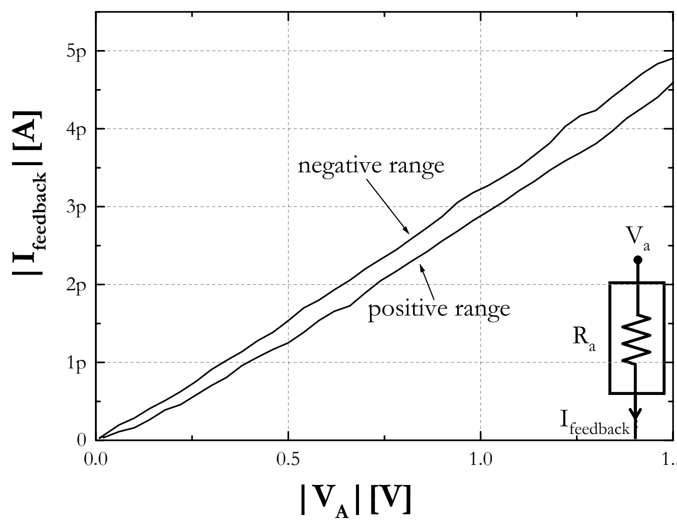

Figure 8.7.4: I-V characteristic for R_a.

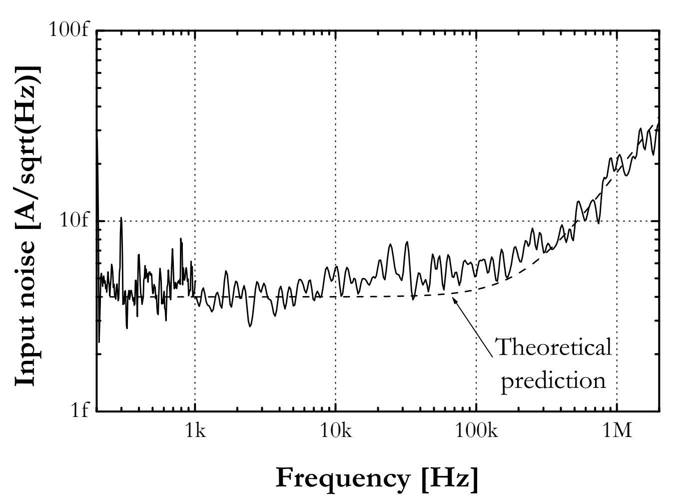

Figure 8.7.5: Measured input noise for the prototype shown in Fig. 8.7.1.

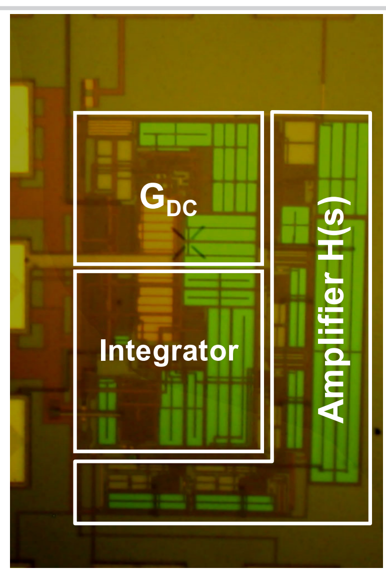

Figure 8.7.6: Chip micrograph.

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